A Dynamic Process Model of Bipolar Disorder States Switching Based on the Salience Network

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Abstract

Bipolar disorder is a highly burdensome and refractory mental disorder, affecting individuals, families, and society. The challenge in bipolar disorder is that the treatment targeting the depressive state often carries the risk of inducing manic state, and vice versa, with the frequency of these alternating cycles often indicating the severity of the illness. Therefore, reducing the frequency of states switching in bipolar disorder patients and gradually achieving a stable state are crucial for effective treatment. The purpose of this study is to propose a dynamic process model of bipolar disorder states switching in order to further understand the treatment, patterns of occurrence and development, and pathophysiological mechanisms of bipolar disorder. Considering the remarkable potential of the salience network in brain switching, we have anchored the model on the functionality of the salience network and analyzed and demonstrated the pathways involved in bipolar disorder states switching within the framework of "physiological-psychological-neurological". By focusing on the salience network, this model provides valuable insights into the mechanisms underlying bipolar disorder states switching.

Keywords: bipolar disorder; disease progression; model; switching; salience network.

Introduction

Bipolar disorder (BD) is a severe mental illness that imposes significant burdens on individuals, families, and society.[1-4] The underlying mechanisms of this disorder are still not fully understood, and its symptoms are highly complex. Rather than being definitive, the symptoms of BD involve a cyclic alternation between a series of depressive symptoms and a series of manic symptoms.[5,6] Our previous work has shown that the manic and depressive states of BD may have different pathological mechanisms.[7-9] This suggests that different treatment and intervention strategies should be employed for the different states of BD patients. However, the treatment challenge lies in the ease with which bipolar patients transition from depressive to manic or from manic to depressive state.[10] Treatment targeting the depressive state often carries the risk of inducing manic state, and vice versa.[10-15] Moreover, the frequency of these alternating cycles often indicates the severity of the disease.[16,17] To investigate the mechanisms of BD states transitions and reduce the frequency of state changes in bipolar patients to achieve a stable state, researchers have identified various factors that influence BD state changes. We summarized these factors into four categories: genes, external events, neurotransmitters, and large-scale functional brain networks, and discussed their mechanisms of action. Clearly, these factors constitute a multidimensional framework of "physiological-psychological-neurological" dimensions that influence the onset and development of BD. While researchers agree that multiple factors contribute to BD,[10,12,18] few have discussed them within a multidimensional framework. Additionally, symptom switching is a key feature of BD, yet we still lack a comprehensive understanding of the processes underlying BD states switching, which is considered the "holy grail of BD research".[12] Analyzing the process of BD states transitions will contribute to the prediction and treatment of BD patients.[19]

To address this, we propose a dynamic process model for BD states switching. In this model, we integrate the most consistent findings about BD along with our own work on the subject in an attempt to elucidate the process of BD states transitions.

Potential mechanisms of states switching

Genes

In the investigation of the underlying mechanisms of BD, it is crucial to constantly bear in mind that it is a genetically based disorder. The genetics of BD has been extensively discussed in previous reviews,[20,21] and numerous genome-wide association studies (GWAS) have also revealed many risk genes.[22-27] In our previous studies, we have confirmed some risk genes such as ANK3 through genetic imaging research and found that clock genes such as RORB already start to affect circadian rhythms during childhood and adolescence.[28] In this study, we reviewed several risk genes associated with states switching in BD and elucidated their impact on the cycling of BD states.

Studies have found that ANK3, in addition to being one of the most prominent risk genes in BD, also provides insights into the emotional transitions observed in BD. For example, researchers have observed that mice with ANK3 heterozygous or ANK3 homozygous deletions exhibited manic-like behaviors at baseline levels, such as hyperactivity, and demonstrated depression-related behaviors under chronic stressors such as repeated social defeat.[29,30] Another risk gene contributing to bipolar mood transitions is Synaptotagmin-7 (Syt7). Shen et al. found that Syt7 deficiency led to behavioral fluctuations in mice, characterized by prolonged periods of

immobility under light conditions and shorter periods of immobility under dark conditions across various behavioral tests.[31] This mimicked the circadian rhythm characteristics observed in patients with BD. Coincidentally, Syt7 knockout mice also exhibited disrupted circadian rhythms.[31] The disruption of circadian rhythms is particularly relevant in the clinical assessment of patients with BD as it often serves as a precursor to mood transitions. The single nucleotide polymorphisms (SNPs) of circadian rhythm genes Period3 and ARNTL, as well as the circadian output rhythm control genes CLOCK and GSK3 β, have been shown to be associated with symptoms related to BD.[32,33] These genes collectively contribute to the understanding of states switching in BD. In addition, the Val66Met polymorphism of the brain-derived neurotrophic factor (BDNF) gene, although not specifically associated with circadian rhythms, has been found to be particularly related to rapid cycling in BD.[34,35]

Indeed, in BD, genetic factors may influence emotional switching through two pathways. First, genes regulate the perception of internal and external stimuli in BD patients, thereby broadly influencing symptoms such as emotions, cognition, motivation, and physical manifestations.[36-38] Second, mediated by neurotransmitters. Aberrant gene expression affects the production, release, transmission, binding, and reuptake of specific neurotransmitters, thereby influencing the physiological processes in the brain such as development, behavioral manifestations, and psychiatric disorders.[39-42] Exploring these processes would deepen our understanding of the pathophysiology of BD and its mechanisms.

External events

The etiology and clinical course of BD are often believed to be determined by a combination of genetic factors and a wide range of external events.[43] These broad external events include infection, climate change, childhood trauma, social support, and others.[44-47] We would like to emphasize the impact of stressors on individuals with BD, such as unemployment, exams, and changes in interpersonal relationships, as well as any acute stimuli that may induce stress and emotional responses. Studies have found that positive life events and achievement of goals were often observed prior to the onset of mania, while negative life events were often associated with depression.[48,43] Our research has also revealed that BD patients in different states exhibit different neural responses to the same emotional stimuli.[8]

External events not only have the potential to directly trigger emotional changes, but more importantly, they may disrupt neurotransmitter systems,[49] leading to a level of mood cycling that aligns with the manifestation of psychiatric disorders, such as BD.[50] Report from Science have confirmed that neurotransmitter transitions in the adult brain can be achieved through natural sensory stimuli, further regulating behavior.[51] And, the kindling hypothesis of mood disorders suggests that this process may become increasingly spontaneous.[52] Furthermore, stress-induced alterations in the immune system can have an impact on the neurotransmitter system through immune dysregulation and subsequent inflammation.[49] Therefore, the occurrence of various unexpected life events in the lives of individuals with BD can serve as strong predictive factors for their states transitions and have significant implications for treatment. It should be noted that medication use, as one of the most common treatment approaches, directly alters the physiological processes involved in neurotransmitter signaling in the brain and should be considered separately.

Neurotransmitters

The neurotransmitter hypothesis of BD states switching has long been established. We have summarized several key neurotransmitters that are highly relevant to BD mood states and attempted to categorize them as predictive factors for mood states switching. Among them, neurotransmitters such as dopamine (DA), serotonin (5-HT), and norepinephrine (NE), which are involved in combating depression and can significantly induce manic emotions. For instance, clinical studies have demonstrated that tricyclic antidepressants, ketamine, and levodopa effectively alleviate depressive symptoms in patients by increasing the levels of 5-HT, NE, or DA.[53-55] Moreover, when used in the treatment of BD, these medications can induce transitions to a manic state to varying degrees.[12] Another key neurotransmitter that can induce transitions from mania to depression in BD patients is acetylcholine. Van Enkhuizen et al. simulated the depressive state of BD in mice by elevating acetylcholine levels.[15] In addition to medication use, the risk genes and life events mentioned earlier can also induce changes in neurotransmitter levels, thereby mediating states transitions in individuals with BD.

However, further investigation is warranted to explore how neurotransmitter dysregulation mediates changes in BD states. We posited that neurotransmitter dysregulation further leads to abnormalities in large-scale functional brain networks, including both within-network dysregulation and between-network dysconnectivity. These abnormalities in functional brain networks further characterize the diverse symptoms observed in individuals with BD. We provided a detailed description below.

Large-scale functional brain networks

Since the discovery by B. T. Thomas Yeo of functional networks inherent in the human cerebral cortex through intrinsic functional connectivity,[56] there is growing evidence that people's emotional and cognitive functions are closely related to intrinsic functional networks.[57-60] In contrast to being limited to some specific cortical or subcortical brain areas, Luiz Pessoa suggested that emotions should be understood in terms of the interaction of large-scale networks.[61] Several researchers have defined different states of BD patients through functional coupling between networks. A recent review of studies on the mechanisms of BD found that combinations of different states of functional activity of brain networks may lead to a different set of symptoms that may correspond to a more refined subtype classification of BD.[62] They found that when the default mode network (DMN), sensorimotor network (SMN), and salience network (SN) activities were consistently enhanced, it led to a manic state in BD, while when all three activities were consistently diminished it led to depression. Furthermore, when DMN activation is reduced and SMN and SN activation is increased, it leads to manic symptoms with negative thinking and, conversely, depressive symptoms with euphoric thinking. These results suggest that changes in the large-scale brain network of BD patients may be responsible for the recurrence of their different symptoms. While there is limited validation for these hypotheses, it is an undisputed fact that BD patients exhibit impairments in large-scale brain networks. Our previous studies have demonstrated extensive structural or functional impairments in networks such as the DMN, SMN, SN, central executive network (CEN), and language network (LaN) in BD patients,[63-65] which profoundly affect the balance between brain networks.[65] The distribution of these networks in the brain can be visualized in Figure 1.

In conclusion, we conducted a comprehensive review of potential mechanisms influencing states transitions in individuals with BD, considering various levels including physiological,

psychological, and neural factors. And it is beneficial for exploring the pathophysiology of BD to establish connections among these factors. Several researchers have made attempts in this direction. For exemple, Magioncalda and Martino combined physiological and neural factors to propose a unified model of the pathophysiology of BD.[66] They suggested that white matter alterations caused by immune dysregulation result in damage to the limbic network, disrupting the stability of neurotransmitter signaling and disrupting the balance between large-scale brain networks, ultimately leading to various phenotypes of BD. However, the consistent and long-term nature of white matter damage is incompatible with the richness and rapid fluctuations of BD symptoms. To explain the cyclic episodes of depression and mania in BD patients, we should proceed to develop a dynamic model. Furthermore, previous models have primarily focused on characterizing the symptoms of BD. However, the process of BD states transitions have been overlooked. We are still unclear about how the transitions between depression and mania occur in BD. Clarifying this key aspect may help us better distinguish BD from unipolar depression and other mental disorders. It is crucial for uncovering the essence of BD.

Considering the unique role of SN in this regard, we have integrated physiological, psychological, and neural factors in an attempt to establish a dynamic process model of BD states switching based on SN. We have provided specific elaboration on this topic below.

Modeling of BD states switching

SN: the core network in BD

Abnormal SN function is frequently found in patients with BD,[64] and a causal analysis of brain networks across multiple disorders found that increased self-inhibitory connectivity of SN is a disorder-specific pattern for BD.[67] A study on the functional segregation, integration, and balance of BD networks has also found that SN is a functional network that effectively predicts BD mood symptoms.[68] More importantly, the SN has been demonstrated to exhibit exceptional potential in “brain switching”. Since Vinod Menon proposed the triple network (TPN) model,[69] it has been validated and widely applied in the field of mental disorders.[70-73] The TPN model primarily describes the relationship between the SN, CEN, and DMN. Its main proposition is that the SN, through key nodes such as the anterior insula (AI) and anterior cingulate cortex (ACC), facilitates the switching of brain functions between the DMN and CEN.[69] Researchers also identified unique neurons present only in the SN, the von Economo, which are present in the AI and facilitate the process of network switching.[74-77] Due to the prominent role of AI, people tend to focus on the cortical nodes when studying the function of SN. However, since the discovery and proposal of the SN as an important functional network in humans, it has been recognized as a set of brain regions that involve both cortical and subcortical interactions.[78] A comprehensive consideration of the interactions between various brain regions within the SN and their roles in information input and output helps us to better understand the impact of SN abnormalities on mental disorders.

The SN, including key cortical and subcortical brain regions such as the AI, dorsal anterior cingulate cortex (dACC), thalamus, amygdala, substantia nigra (SuN) and ventral tegmental area (VTA), involves in perceiving and responding to the brain's homeostatic demands.[78,76,69,75] The insular cortex plays a central role in detecting behaviorally relevant stimuli and coordinating neural resources, and the atypical involvement of specific subregions of the insula within the SN is a characteristic feature of many neuropsychiatric disorders.[76] For example, the AI cortex receives

incoming signals from both internal bodily sensations and external stimuli, and it performs a relative salience detection to determine the allocation of brain resources.[76,79] In BD patients, abnormalities in AI can lead to disturbances in salience detection, which further result in altered functional coupling across the whole brain. For example, the ACC is connected to the motor systems and receives signals from the AI to output responses related to visceral, autonomic, behavioral, and cognitive processes, constituting the behavioral phenomenology of BD.[62,73,75] Additionally, according to the TPN model, the weakened connectivity of the insula and cingulate can lead to aberrant involvement of the frontoparietal CEN, impairing adaptive behaviors related to cognition and goals. Significant events affecting the DMN can also result in alterations in self-referential mental activity. Furthermore, the SN has significant influence on the LaN as well.[73,80] Researchers have found that disrupted excitatory-inhibitory balance in the cingulate-insular, lateral prefrontal cortex, and superior/middle temporal regions at the synaptic level can lead to structural and functional changes locally and across networks, thereby impacting the dynamic representation of linguistic elements.[80] According to the DSM-5, language disturbance is also a prominent feature used for diagnosing individuals with BD. On the other hand, the representation of BD symptoms by subcortical nodes in SN is more related to neurotransmitters. The VTA, rich in DA and 5-HT neurons, serves as a significant source region within the dopaminergic neural pathway. Another region containing DA neurons is the SuN. Studies have found that enhanced dopamine signaling strengthens the coupling between the thalamus and SMN, and increases the activity of SMN.[81,82] In addition to being regulated by DA, the thalamus is capable of directly receiving sensory inputs from the external environment and sending outputs to the motor systems of the body.[83,84] Threat salience stimuli in the external environment are also detected by the amygdala and produce corresponding emotional and behavioral responses.[85,86] Furthermore, similar to the VTA, the amygdala is also a site of 5-HT production. Studies have indicated a close relationship between the severity of depression and a decrease in amygdala 5-HT.[87] And increased 5-HT levels can inhibit the activation of DMN.[88] In addition, the amygdala, VTA, and ACC are all part of the reward circuitry. The strong signals from the amygdala and VTA can be transmitted to the SMN via the ACC, and the excessive activation of the SMN can lead to highly motivated impulsive behavior.[89] And, the VTA and SuN can project to the frontal lobe of the cerebral cortex via the mesocortical pathway and the substantia nigra reticularis, respectively, the inhibitory or excitatory modulation of dopamine-related prefrontal brain regions can influence higher cognitive functions.[90]

In summary, we hypothesized that the SN is the core network mediating states switching in BD. The functional abnormalities in the SN lead to a distorted perception of external and internal information in individuals with BD. This accelerates the cycling and disruption of bipolar symptoms. The accompanying neurotransmitter imbalances further contribute to this process, and medication is often used to counteract this imbalance. It is noteworthy that these processes are influenced by genetic factors, as susceptibility genes modulate neurotransmitter systems and the brain's sensitivity to internal and external stimuli. In order to better understand the mechanisms of BD states switching, we propose a dynamic process model describing BD states switching based on SN, integrating physiological, psychological, and neural network factors.

Dynamic process model based on SN

The schematic diagram of the model is shown in Figure 2. Since the described process of BD

states transitions in the model dynamically changes based on different stimulus information, we refer to this model as the “Dynamic process model”. It was proposed based on the function of SN.

Specifically, abnormal functioning of SN leads to impaired significance detection in BD patients, making them more likely to detect negative or positive events in their daily lives and perceive them as more important information. Risk genes regulate physiological processes such as susceptibility to internal and external stimuli and neurotransmitter synthesis. When individuals with BD experience positive internal and external stimuli in their daily lives, the AI-ACC pathway promotes excessive activation of the SMN and shifts the DMN-CEN from a balanced state to a low-activity DMN and overactive CEN state. Simultaneously, the disrupted balance between the AI-ACC and the superior and middle temporal areas and the lateral prefrontal cortex leads to dysfunction in the language network. The thalamic pathway and the VTA-SuN-thalamic pathway together contribute to the hyperactivation of the SMN. The VTA-SuN pathway leads to excessive activation of the prefrontal cortex, which is involved in cognitive functions. These regions are not an intrinsic brain network but rather specific parts of the frontal lobe associated with DA. The influence of the amygdala-VTA on the ACC also facilitates the SN in shifting the brain's networks into a state of excessive activation. As a result, BD patients transition into a manic state (Fig. 3A). On the contrary, when individuals with BD experience negative internal or external events, these pathways will instead inhibit the corresponding brain activity, leading to a transition into a depressive state (Fig. 3A). When there is a conflict between internal and external information (such as positive external events and negative internal experiences, or negative external events and positive internal experiences), BD patients may enter a mixed state or experience rapid cycling between mood states. In addition, pharmacotherapy regulates physiological processes such as neurotransmitter synthesis. This has a direct and wide-ranging effect on patients with BD, but this is often accompanied by the risk of causing states switching.

According to this model, the transition of BD patients between states is dynamic and requires continuous accumulation of internal and external inputs. The cumulative stimuli reach a certain stage, leading to a significant shift in the detection by the SN (from negative to positive salience or from positive to negative salience), which in turn causes the transition of BD states. This reminds us that the depressive and manic phases of BD are not discrete states, and their transition represents a continuous process (Fig. 3B). Therefore, we speculate that there might be a sensitive period for state transitions between stable depressive and manic states in BD patients, accompanied by a greater risk of accelerated switching (Fig. 3B). This sensitive period may be a period of mixed symptoms or a period of symptomatic remission, which may depend on the functional status of the SN. Previous studies have indicated that despite the abnormal functional connectivity observed in motor areas, DMN, and CEN in euthymic BD patients, normal SN function may mediate BD patients entry into a state of remission.[91]

In summary, our dynamic process model describes the mechanisms of BD state transitions within a multidimensional framework of physiology, psychology, and neurology. The model emphasizes the critical role of the SN, and the aberrations in these processes align with the symptoms observed in BD patients.

Clinical implications and future directions

The strengths of the BD states switching dynamic process model lie in its comprehensive integration of the physiological, psychological, and neural perspectives, which elucidates the

pathological processes underlying BD states transitions and their correspondence with major clinical manifestations. In addition, located in the central part of the brain and consisting of key structures both on the cortical and subcortical levels, the SN serves as a natural bridge connecting various functional regions of the brain (Fig.1). Without building the model on the foundation of SN, it would be challenging to provide a comprehensive description of the pathological processes underlying BD states transitions.

Reducing the frequency of BD states transitions and achieving gradual stability has always been a challenging task in treatment. From this model, it can be observed that external events influence BD state changes through multiple pathways. Therefore, we consider external events to be important triggering factors influencing BD states transitions. The atypical perception of external stimuli by SN, regulated by genetic factors, serves as the catalyst for BD states transitions. Therefore, when treating BD patients, special attention should be paid to the various events occurring in their lives. Creating different types of events can be used as an adjunctive approach to counteract BD episodes and help patients gradually achieve a stable state of relief. For instance, a recent study has shown that sleep deprivation enhances the connectivity between the amygdala and ACC, leading to improved mood in individuals with depression.[92] Furthermore, medication treatment for BD patients should take into account the practical aspects of their lives and be adjusted flexibly.

Our model also deduces a sensitive period of states switching during the development of BD, which could be beneficial for the treatment of patients. Due to the increased risk of state transitions during the sensitive period, the treatment approach for BD patients in this phase should be cautious, conservative, individualized, and promptly adjusted. Regarding the treatment of euthymic BD patients, the focus can be shifted towards stabilizing and maintaining SN function, rather than continuing medication solely targeting depressive or manic symptoms. For example, in ethically approved cases, non-pharmacological treatment methods such as psychotherapy or transcranial magnetic stimulation (TMS) can be utilized to indirectly improve SN function.

And, in the future, this model may potentially be expanded to other psychiatric disorders for further applications. Any psychiatric disorder can be described as a transition from a normal state to a pathological state. The establishment of this model may provide valuable insights for developing pathological transition models for other psychiatric disorders.

However, we currently lack a precise description of the timing of BD patient's state transitions. The exact moment when SN's significance prediction changes and subsequently mediates the state transition remains unclear. While we have identified a sensitive period, it is still insufficient for fully understanding the mechanisms underlying BD. Further research is needed to gain a more comprehensive understanding of BD and its dynamics. Future research should also focus on identifying the sensitive period in BD. Methods such as machine learning should be applied to individualize classification and identify sensitive periods in patients, which can have positive implications for treatment.

Finally, our model focuses on the processes and mechanisms of states switching in patients with BD. This is limited for a comprehensive description of the pathophysiological mechanisms of BD. In the future, various models of BD development should be constructed and synthesized to better understand BD.

Conclusion

In the framework of "physiological-psychological-neurological", we have proposed a dynamic process model of BD states switching based on the functionality of the SN. This model provides a detailed description of the pathways involved in the transition from depression to mania or from mania to depression in BD and infers a sensitive period for the states switching. We also emphasize the significant role of external events as triggering factors. Our model contributes to a better understanding of the underlying mechanisms, diagnosis, treatment, and prediction of BD.

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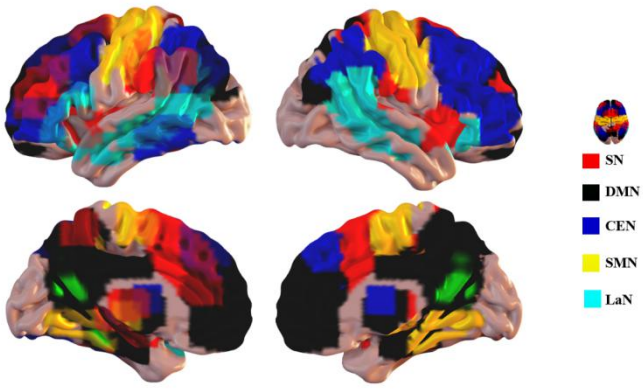

Fig.1 Distribution of major networks in the brain. Abbreviation: SN salience network, DMN default mode network, CEN central executive network, SMN sensorimotor network, LaN language network. And the brain maps were built by Surf Ice (https://www.nitrc.org/projects/surfice).

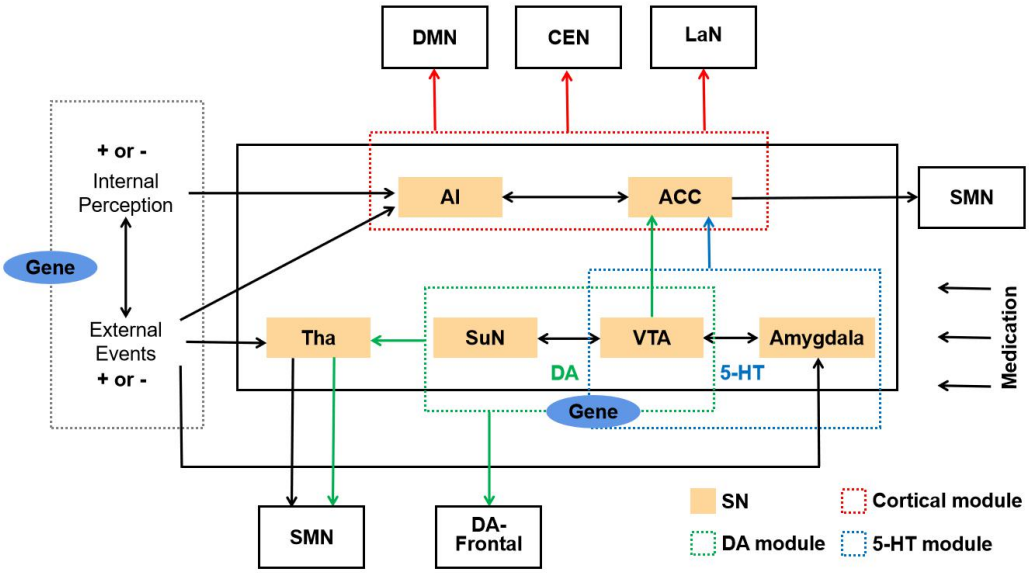

Fig.2 The Dynamic Process Model of Bipolar Disorder States Switching Based on the Salience Network. Under genetic regulation, SN receives stimuli and neurotransmitter modulation from internal and external sources, affecting major brain functional networks and functional areas and facilitating BD states switching. Positive internal and external stimuli prompted the SN to cause hyperactivation of the CEN, SMN, LaN, DA-related frontal lobes and suppression of DMN activity, and patients with BD entered a manic state. Conversely, BD patients enter a depressive state. Stimuli of different potency cause disorganization of the BD states (mixed or rapid cycling). Medicines can provide direct modulation of these pathologies. Abbreviation: SN salience network, AI anterior insula, ACC anterior cingulate cortex, Tha thalamus, SuN substantia nigra, VTA ventral tegmental area, DA dopamine, 5-HT serotonin, DMN default mode network, CEN central executive network, SMN sensorimotor network, LaN language network, DA-Frontal frontal brain regions associated with dopamine, + positive, - negative.

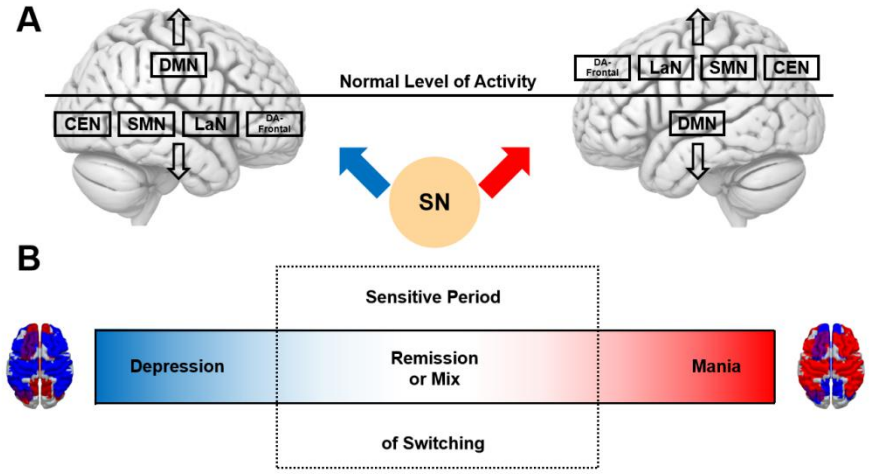

Fig.3 Switching between depression and mania in BD is a continuous process. (A) SN regulates the activity of major brain networks. Depressive state on the left, manic state on the right. (B) There is a switch-sensitive period during the switch between depression and mania in BD patients. This period is accompanied by a greater risk of switching. Abbreviation: SN salience network, DMN default mode network, CEN central executive network, SMN sensorimotor network, LaN language network, DA-Frontal frontal brain regions associated with dopamine.